Analysis of the expression of NANOS and PUMILIO proteins and epithelial-mesenchymal transition markers in gastroenteropancreatic neuroendocrine tumors with the use of artificial intelligence-assisted digital image analysis

Neoplastic diseases are the second most common cause of death in Poland and their number has nearly doubled over the last thirty years. However, neoplasm is not a single clinical entity, as it was thought years back, but rather a heterogenous group of clinical entities characterized by different clinical behavior and prognosis. Due to the fact that neoplasms may have this different clinical behavior and prognosis and are therefore classified into benign (usually limited to the tissue of origin without any capability to invade the surrounding tissues or to metastasize) and malignant (characterized by their propensity to invade the surrounding tissues and capability to metastasize).

Metastasis is a complex and not yet understood process. During metastasis single cells detach from the primary tumor, enter the blood or lymphatic vessels and settle within different, sometimes distant, tissues. Presence of metastases signifies worse prognosis in cancer patients and therefore understanding the process is of crucial importance.

It is suggested that epithelial-mesenchymal transition plays a role in metastasis. It is a process that was initially described during embryonic development and later it was discovered it is also employed by the neoplastic cells. During epithelial-mesenchymal transition stationary neoplastic cells interconnected with the surrounding cells change into cells with a migratory capability.

Several proteins have been described to be involved in the epithelial-mesenchymal transition (e.g. SNAIL, TWIST). However, recent studies show that other proteins may be involved in the process – NANOS and PUMILIO proteins.

The aim of our study is to find out whether NANOS and PUMILIO proteins are involved in the epithelial mesenchymal transition. To do that we intend to use gastroenteropancreatic neuroendocrine tumors (GEP-NETs), neoplasms derived from the neuroendocrine cells of the gastrointestinal tract and the pancreas. Using the proteins already known to be involved in the epithelial-mesenchymal transition, we are going to identify the tumors that activate the epithelial-mesenchymal program. Then, we are going to compare the expression of NANOS and PUMILIO proteins in those tumors that do activate the epithelial-mesenchymal transition program and those that do not. Understanding the role of NANOS and PUMILIO proteins may aid in identification of new signaling pathways that in the future may be used to design targeted drug therapy.

We decided to use gastroenteropancreatic neuroendocrine tumors to study for several reasons. First of all, we have a reasonable group of such patients under our care in the hospital and it is well-described in the literature that GEP-NETs do activate epithelial mesenchymal program. Second of all, NANOS and PUMILIO have been described in neoplastic tissues only in lung cancer, and hence checking their expression in different neoplasms may help to indirectly answer the question whether those proteins might universally be involved in the neoplastic process. Lastly, the study may aid the GEP-NETs patients themselves. GEP-NETs are actually a heterogenous group – some behave as benign neoplasms, and some as malignant with a tendency to metastasize. If NANOS and PUMILIO proteins were found to be involved in epithelial-mesenchymal transition, this would mean that it is plausible they would also be involved in the process of metastasis of GEP-NETs, and hence they could be used as potential markers of this group of patients. This could help in identifying at-risk patient groups that would require different diagnostic and therapeutic approaches.